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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/704,159	08/28/1996	JAMES A. WILLIAMS	OPHD-02304	8816

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EXAMINER
LI, BAO Q

ART UNIT	PAPER NUMBER
1648	43

DATE MAILED: 11/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	08/704,159	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *42,43,54-57,79,80,89-91,93,94,100,103-105 and 107-112*.

   Claim(s) withdrawn from consideration: *None*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: *Interview summary*

Bao Qun Li

Advisory Action

Terminal disclaimer filed under 37 CFR 3.739b) has been acknowledged.

The response to the final action filed on 09/11/2002 under 37 CFR 1.116 has been entered. Claims 44-53, 58-63, 66-78, 81, 82, 84, 85, 87, 95, 96, 98, 99, 101, 102 have been canceled. Claims 42, 43, 54-57, 79-80, 86, 89-91, 93-94, 100, 103-105, 107-109 and 110-112 within the scope of clostridium botulinum toxin A are pending. The request for reconsideration has been considered; however, the claims as they are filed are not deemed to place the application in condition for allowance.

For purpose of appeal, the status of the claims is as follows:

Allowed claim(s): NONE.

Rejected claim (s): 42, 43, 54-57, 79-80, 86, 89-91, 93-94, 100, 103-105, 107-109 and 110-112 within the scope of clostridium botulinum toxin A.

Claim(s) objected to: NONE.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42-43, 54-57, 79-80, 83, 86, 89-91, 93-94, 100, 103-105 and 107-109 are still rejected under 35 U.S.C. 103(a) on the same ground as stated in the previous office action as being unpatentable over Thompson et al. (Eur. J. Biochem. 1990, Vol. 189, pp. 73-81), Dobeli et al. (US Patent No. 5,310,663) and Ford et al. (Protein Expression and purification 1991, Vol. 2, pp. 95-107) on the same ground as stated in the previous office action.

Applicants argue that there is no motivation to combine the reference because in nowhere the reference teaches to make a recombination botulinum toxin protein in a soluble form with a reasonable expectation of success.

Applicants' argument has been respectfully considered. However it is not found persuasive because the claimed invention is not a method for making a soluble recombinant botulinum toxin protein but rather a product of a botulinum toxin protein.

The Declaration under CFR 1.132, paper NO. 37, filed 05/28/02 have been considered fully, but they are not persuasive to overcome the 103 rejection because the claimed invention is a product, which has same functional structural and function properties as it is disclosed in the prior art. The declaration by Dr. William argues that they used a special promoter to increase the solubility of the recombinant fusion protein of C botulinum type A solubility. This may be a method for making the product, which does not make the claimed product structurally and functionally distinct from the product disclosed in the cited prior art. Therefore, it cannot be used as the evidence to overcome the obvious type prior art rejection. The rejection maintained.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54, 93 and 110-112 are still rejected under 35 U.S.C. 112, first paragraph on the same ground as stated in the previous office action, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant disclosure, the applicants have only disclosed that certain fragments of clostridium botulinum toxin as defined as clones pMA660-110, ppPA 1100-1450, pPA1100-1870, which are able to be expressed as a soluble fusion protein when the particular pET23 vector or pMALc vector are used. No other sequences, which having at lease 4 amino acid

residues of any or all clostridium botulinum toxin, is disclosed to be able to expressed as a soluble fusion protein.

Applicants argue that the present claims are directed to sequences that are well known in the art at the time of filling. Thus, the practitioner of ordinary skill is able to obtain the information. The University of California V. Eli lilly and Co. cited by the examiner is not applicable in the present case because in Eli illy, the court ruled that a claim cannot be made an unknown cDNA sequence by applicant who has only disclosed a potential method o isolating such sequence, even though the method has been used by applicant to isolate a homology cDNA sequence from a different organism.

Applicants' argument has been respectfully considered; however, it is not found persuasive because while the sequences of the clostridium botulinum toxins are known in the art, specification does not teach what are the metes and bounds of the sequences encompassing any or all 4 amino acid residues of any or all clostridium botulinum toxin, there is not enough information about it in literature either to guide the one of ordinary skill in the art to predict the undisclosed any or all random selected 4 amino acid residues from any or all clostridium botulinum toxin. The new sequence derived from the any or all random selected 4 amino acid residues from any or all clostridium botulinum toxin is an unknown sequence, which assemble the situation of *University of California v. Eli Lilly and Co.*, which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism. 35 USC 112 requires inter alia that "a patent specification contain a written description of the invention and the manner and process of making and using it in such full clear and concise terms as to enable one skilled in the art to make and use the invention".

Applicants are reminded that 35 USC 112 requires inter alia that "a patent specification contain a written description of the invention and the manner and process of making and using it in such full clear and concise terms as to enable one skilled in the art to make and use the invention". Case law has made it clear that the requirements for a "written description" and an "enabling disclosure" are separate. For example, where a specification contains sufficient

information to enable a skilled chemist to produce a particular compound because it gives detailed information on how to produce analogous compounds but it makes no reference to the compound in question, the "written description" requirement has not been met even though the description may be enabling.

Claim Rejections - 35 USC § 112

Claims 42-43, 54-57, 79-80, 83, 86, 89-91, 93-94, 100, 103-105, 107-109 and 110-112 are still rejected under 35 U.S.C. 112, first paragraph, under the same ground as stated in the previous office action because the specification, while being enabling for having certain fragments of clostridium botuluninum toxin A as defined as clones pMA660-110, ppPA 1100-1450, pPA1100-1870, which are able to be expressed as a soluble fusion protein when the particular pET23 vector or pMALc vector are used, does not reasonably provide enablement for having any or all random selected fragments of the clostridium botulinumn toxin sized from 4 amino acid residues to the full length of any or all clostridium botulinum toxin made as a soluble fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants argue that the present specification fully discloses the use of a week promoter, among other things, including chaperone mediated folding of recombinant proteins, produce soluble recombinant botulinum toxin protein.

Applicants are reminded that the test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988).

In the instant case, although it is well know in the state of the art that any protein can be engineered to expressed as a fusion protein. However, it is always unpredictable the solubility of the fusion protein when it is finally expressed. There are multiple factors that influence the

solubility of the fusion protein. The specification only teach certain fragments of clostridium botulinum toxin A clones pMA660-110, ppPA 1100-1450, pPA1100-1870, which is suitable to be expressed as a soluble fusion protein when they are carried by the pET23 vector and pMALc vector.

The specification is deficient for teaching how to select the fragment ranged from size at least four amino acids to full length minus one of any or all the clostridium botulinum toxin and it does provide any guidance how to select those sequences.

Therefore, considering the scope so broadly read on any or all fragments sized from 4 amino acids to the full length of the amino acids minus 1 of any or all clostridium botulinum toxin, it concluded that undue experimentation would have been required for the person skilled in the art to make and practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42-43 are still rejected under 35 U.S.C. 102(b) on the same ground as stated in the previous Office Action, as being anticipated by Lapenotiere et al. (Toxicon, 1995, Vol. 33, pp. 1383-1386).

Applicants admitted that Lapenotiere et al. disclose a method for using the recombinant technique to express a large, nontoxic fragment of botulinum neurotoxin serotype A and the isolated nontoxic fragment of botulinum neurotoxin serotype A. However, the final product of the recombinant fragment of botulinum neurotoxin serotype A is in an insoluble form.

Applicants' argument has been respectfully considered; however, it is not found persuasive because although the product is initially expressed in an insoluble form, after renaturation process, the final product of the recombinant botulinum neurotoxin is a soluble protein. Therefore, the rejection is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li
October 22, 2002

James C. Housel
JAMES HOUSEL 11/3/02
SUPERVISORY PATENT EXAMINER
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